Access DB# 83281

SEARCH REQUEST FORM

Scientific and Technical Information Center

Requester's Full Name: BEN JACKEY Examiner #: 73089 Date: 12/30/02
Art Unit: 1626 Phone Number 305-6867 Serial Number: 10/031,412
Mail Box and Bldg/Room Location: CM1 3F11 Results Format Preferred (circle): PAPER DISK E-MAIL

If more than one search is submitted, please prioritize searches in order of need.

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Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: Bases for the preparation of naproxone nitroxyalkylesters

Inventors (please provide full names): Brine Divi et al

Earliest Priority Filing Date: 8/4/99

**For Sequence Searches Only* Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.*

process for preparing nitroxyalkylesters of formula A-O-Y-ONO2 as defined in the claims in the presence of an inorganic base.

A → an acyl residue

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STAFF USE ONLY	Type of Search	Vendors and cost where applicable
Searcher: K. Fisher	NA Sequence (#)	STN ✓
Searcher Phone #:	AA Sequence (#)	Dialog
Searcher Location:	Structure (#) 1	Questel/Orbit
Date Searcher Picked Up:	Bibliographic	Dr.Link
Date Completed: 1/21/03	Litigation	Lexis/Nexis
Searcher Prep & Review Time: 20	Fulltext	Sequence Systems
Clerical Prep Time:	Patent Family	WWW/Internet
Online Time: 14	Other	Other (specify)

PTO-1590 (8-01)

=> file reg
FILE 'REGISTRY' ENTERED AT 16:25:07 ON 21 JAN 2003
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 20 JAN 2003 HIGHEST RN 479577-81-6
DICTIONARY FILE UPDATES: 20 JAN 2003 HIGHEST RN 479577-81-6

TSCA INFORMATION NOW CURRENT THROUGH MAY 20, 2002

Please note that search-term pricing does apply when conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

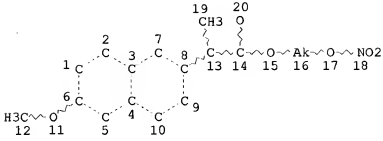
Experimental and calculated property data are now available. See HELP PROPERTIES for more information. See STNote 27, Searching Properties in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

=> file hcaplus
FILE 'HCAPLUS' ENTERED AT 16:25:13 ON 21 JAN 2003
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

FILE COVERS 1907 - 21 Jan 2003 VOL 138 ISS 4
FILE LAST UPDATED: 20 Jan 2003 (20030120/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> d que
L5 STR



6 structures from the query which covers naproxene nitroxyalkyl esters

4 preparations

NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 20

STEREO ATTRIBUTES: NONE
L7 6 SEA FILE=REGISTRY SSS FUL L5
L8 17 SEA FILE=HCAPLUS ABB=ON L7
L9 4 SEA FILE=HCAPLUS ABB=ON L8(L)(PREP OR IMF OR SPN)/RL

=> d l9 all 1-4 hitstr

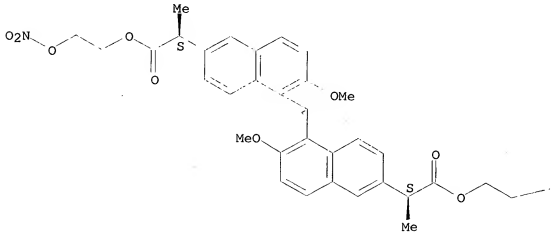
L9 ANSWER 1 OF 4 HCAPLUS COPYRIGHT 2003 ACS
AN 2001:229959 HCAPLUS
DN 135:92422
TI Synthesis and cyclooxygenase inhibitory properties of novel (+) 2-(6-methoxy-2-naphthyl)propanoic acid (naproxen) derivatives
AU Abadi, Ashraf H.; Laufer, Stefan; Lehmann, Jochen
CS Institute of Pharmacy, University of Bonn, Bonn, D-53121, Germany
SO Archiv der Pharmazie (Weinheim, Germany) (2001), 334(3), 104-106
CODEN: ARPMAS; ISSN: 0365-6233
PB Wiley-VCH Verlag GmbH
DT Journal
LA English
CC 25-22 (Benzene, Its Derivatives, and Condensed Benzenoid Compounds)
OS CASREACT 135:92422
AB Halomethylation of naproxen occurs regioselectively in position 5 and subsequently - in situ or on treatment with silver nitrate - leads to naproxen dimers with two naproxen units, 5,5'-connected through a ethenylene and a methylene bridge, resp. Two of the new naproxen derivs. were screened for their cyclooxygenase inhibitory properties relative to naproxen. Both 5-(chloromethyl)naproxen and 2-[5-[(carboxyethyl)-2-methyloxynaphthyl]-6-methoxy-2-naphthyl]propanoic acid were inactive in the concn. range of 0.1-10 .mu.mole against both COX-1 and COX-2, indicating that bulky substituents in position 5 in naproxen are unfavorable for both COX-1 and COX-2 inhibition. The naproxen derivs. thus prepd. were found to be inactive as cyclooxygenase inhibitors.
ST naproxen dimer prepn cyclooxygenase inhibitor
IT 540-51-2, 2-Bromoethanol 22204-53-1, (+)-Naproxen 38483-29-3, 2-Nitroxyethyl bromide
RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn. and cyclooxygenase inhibitory properties of (+)-2-(6-methoxy-2-naphthyl)propanoic acid (naproxen) derivs.)

KATHLEEN FULLER EIC 1700/PARKER LAW 308-4290

IT 349492-87-1P 349492-89-3P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. and cyclooxygenase inhibitory properties of (+)-2-(6-methoxy-2-naphthyl)propanoic acid (naproxen) derivs.)
IT 349492-88-2P 349492-90-6P **349492-91-7P**
RL: **SPN (Synthetic preparation); PREP (Preparation)**
(prepn. and cyclooxygenase inhibitory properties of (+)-2-(6-methoxy-2-naphthyl)propanoic acid (naproxen) derivs.)
RE.CNT 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Allison, M; N Engl J Med 1992, V327, P749 MEDLINE
(2) Anon; Vogel's Textbook of Practical Organic Chemistry, 4th edition 1986, P762
(3) Cook, A; J Chem Soc 1941, P502 HCAPLUS
(4) Davies, N; Aliment Pharmacol Ther 1997, V11, P69 HCAPLUS
(5) Donnely, M; Aliment Pharmacol Ther 1997, V11, P227
(6) Elliott, S; Gastroenterology 1995, V109, P614
(7) Forrest, J; Drug Saf 1997, V16, P309 HCAPLUS
(8) Gierse, J; J Biol Chem 1996, V271, P15810 HCAPLUS
(9) Jackson, L; Drugs 2000, V59, P1207 HCAPLUS
(10) Kartasasmita, E; in preparation
(11) Kawashima, Y; J Med Chem 1993, V36, P815 HCAPLUS
(12) Laufer, S; Arch Pharm Pharm Med Chem 1997, V330, P307 HCAPLUS
(13) Laufer, S; Inflamm Res 1999, V48, P133 HCAPLUS
(14) Singh, G; J Rheumatol 1999, V26, P18
(15) Smith, W; J Biol Chem 1996, V271, P33157 HCAPLUS
(16) Somasundaram, S; Gut 1997, V40, P608 HCAPLUS
(17) Towheed, T; J Rheumatol 1997, V24, P349 HCAPLUS
IT **349492-91-7P**
RL: **SPN (Synthetic preparation); PREP (Preparation)**
(prepn. and cyclooxygenase inhibitory properties of (+)-2-(6-methoxy-2-naphthyl)propanoic acid (naproxen) derivs.)
RN 349492-91-7 HCAPLUS
CN 2-Naphthaleneacetic acid, 5,5'-methylenebis[6-methoxy-.alpha.-methyl-, bis[2-(nitrooxy)ethyl] ester, (.alpha.S,.alpha.'S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B

L9 ANSWER 2 OF 4 HCAPLUS COPYRIGHT 2003 ACS
AN 2001:115100 HCAPLUS
DN 134:178355
TI Process for the preparation of naproxene nitroxyalkyl esters
IN Benedini, Francesca; Oldani, Erminio; Castaldi, Graziano; Tarquini, Antonio
PA Nicox S.A., Fr.
SO PCT Int. Appl., 16 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C07C203-04
CC 25-24 (Benzene, Its Derivatives, and Condensed Benzenoid Compounds)
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001010814	A1	20010215	WO 2000-EP7222	20000727
	W: AE, AL, AU, BA, BB, BG, BR, CA, CN, CR, CU, CZ, DM, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	EP 1200386	A1	20020502	EP 2000-951456	20000727
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
	BR 2000012915	A	20020604	BR 2000-12915	20000727
	NO 2002000515	A	20020201	NO 2002-515	20020201
PRAI	IT 1999-MI1753	A	19990804		
	WO 2000-EP7222	W	20000727		

OS CASREACT 134:178355; MARPAT 134:178355
AB A process for obtaining nitroxyalkyl esters of the 2-(S)-(6-methoxy-2-naphthyl)propanoic acid having an enantiomeric excess higher than or equal to 95 %, preferably higher than or equal to 98 %, was characterized in that a halide of the 2-(S)-(6-methoxy-2-naphthyl)propanoic acid of formula A-Hal, wherein A is the acid acyl residue, is reacted in an inert org. solvent with an aliph. nitroxyalkanol HO-Y-ONO2, wherein Y is a C2-C20 alkylene or a cycloalkylene from 3 to 8 carbon atoms, or an alkylene as

defined contg. a cycloalkylene as defined, in the presence of an inorg. base. E.g., to a soln. of 4-nitroxybutan-1-ol and K2CO3 in dichloromethane is added 2-(S)-(6-methoxy-2-naphthyl)propanoic acid chloride. to give the 4-nitroxybutyl ester of 2-(S)-(6-methoxy-2-naphthyl)-propanoic acid (85%, ee 98%).

ST naproxene nitroxyalkyl ester prepn; naproxen nitroxyalkyl ester prepn

IT **163133-43-5P**
RL: **IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)**
(prepn. of naproxene nitroxyalkyl esters)

IT 22204-53-1, Naproxen 22911-39-3 51091-84-0
RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn. of naproxene nitroxyalkyl esters)

RE.CNT 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

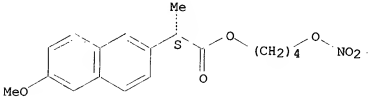
(1) Hoechst Marion Roussel Inc; FR 2757159 A 1998 HCAPLUS
(2) Italfarmaco Spa; WO 9201668 A 1992 HCAPLUS
(3) Nicox Ltd; WO 9509831 A 1995 HCAPLUS
(4) Nicox Ltd; WO 9530641 A 1995 HCAPLUS
(5) Nicox Sa; WO 9716405 A 1997 HCAPLUS

IT **163133-43-5P**
RL: **IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)**
(prepn. of naproxene nitroxyalkyl esters)

RN 163133-43-5 HCAPLUS

CN 2-Naphthaleneacetic acid, 6-methoxy-.alpha.-methyl-, 4-(nitrooxy)butyl ester, (.alpha.S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L9 ANSWER 3 OF 4 HCAPLUS COPYRIGHT 2003 ACS

AN 1998:221441 HCAPLUS

DN 128:226234

TI Nonsteroidal anti-inflammatory agents capable of releasing nitric oxide, their preparing method and use

IN Cai, Xiong; Qian, Changgeng

PA Cai, Xiong, Peop. Rep. China

SO Faming Zhuanli Shenqing Gongkai Shuomingshu, 22 pp.
CODEN: CNXXEV

DT Patent

LA Chinese

IC ICM A61K031-215

CC 1-7 (Pharmacology)
Section cross-reference(s): 25

FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI CN 1144092	A	19970305	CN 1995-109791	19950825
PRAI CN 1995-109791		19950825		

AB The present invention provides a group of nonsteroidal anti-inflammatory

drugs (NSAID) capable of releasing nitric oxide and their nitrates. The NSAID include aspirin, indomethacin, naproxen, brufen, pirprofen, phenol pirprofen, flurbiprofen, ketoprofen, and diclofenac sodium and can be extensively used as antipyretics, analgesics, and antiinflammatory for prevention and treatment of angiocardiopathy and cerebrovascular diseases. The new NSAID nitrates can release nitric oxide in vivo and can reduce the toxicity of NSAID on the digestive tract.

ST antiinflammatory NSAID nitrate prepn nitric oxide

IT Nitrates, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(NASAID; nonsteroidal anti-inflammatory agents capable of releasing nitric oxide, their prepg. method and use)

IT Brain, disease
(cerebrovascular; nonsteroidal anti-inflammatory agents capable of releasing nitric oxide, their prepg. method and use)

IT Cardiovascular system
(disease; nonsteroidal anti-inflammatory agents capable of releasing nitric oxide, their prepg. method and use)

IT Analgesics
Antipyretics
Digestive tract
Toxicity
(nonsteroidal anti-inflammatory agents capable of releasing nitric oxide, their prepg. method and use)

IT Prostaglandins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(nonsteroidal anti-inflammatory agents capable of releasing nitric oxide, their prepg. method and use)

IT Anti-inflammatory agents
(nonsteroidal; nonsteroidal anti-inflammatory agents capable of releasing nitric oxide, their prepg. method and use)

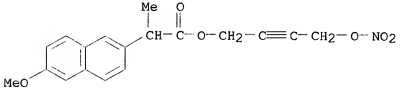
IT 50-78-2, Aspirin 53-86-1, Indomethacin 15687-27-1, Brufen 22204-53-1, Naproxen
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); RACT (Reactant or reagent); USES (Uses)
(nonsteroidal anti-inflammatory agents capable of releasing nitric oxide, their prepg. method and use)

IT 140218-49-1P 204633-00-1P 204633-02-3P 204633-03-4P **204633-04-5P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **SPN (Synthetic preparation)**; THU (Therapeutic use); BIOL (Biological study); **PREP (Preparation)**; USES (Uses)
(nonsteroidal anti-inflammatory agents capable of releasing nitric oxide, their prepg. method and use)

IT 5104-49-4, Flurbiprofen 15307-79-6, Diclofenac sodium 22071-15-4, Ketoprofen 31793-07-4, Pirprofen
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(nonsteroidal anti-inflammatory agents capable of releasing nitric oxide, their prepg. method and use)

IT 10102-43-9, Nitric oxide, biological studies 39391-18-9, Cyclooxygenase
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(nonsteroidal anti-inflammatory agents capable of releasing nitric

oxide, their prepg. method and use)
IT 627-18-9 31121-93-4 204633-01-2
RL: RCT (Reactant); RACT (Reactant or reagent)
(nonsteroidal anti-inflammatory agents capable of releasing nitric oxide, their prepg. method and use)
IT 204632-98-4P 204632-99-5P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(nonsteroidal anti-inflammatory agents capable of releasing nitric oxide, their prepg. method and use)
IT **204633-04-5P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **SPN (Synthetic preparation)**; THU (Therapeutic use); BIOL (Biological study); **PREP (Preparation)**; USES (Uses)
(nonsteroidal anti-inflammatory agents capable of releasing nitric oxide, their prepg. method and use)
RN 204633-04-5 HCAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-.alpha.-methyl-, 4-(nitrooxy)-2-butynyl ester (9CI) (CA INDEX NAME)



L9 ANSWER 4 OF 4 HCAPLUS COPYRIGHT 2003 ACS
AN 1995:667266 HCAPLUS
DN 123:82961
TI Preparation of organic nitrate esters having antiinflammatory and/or analgesic activity
IN Del Soldato, Piero
PA Nicox Ltd., Ire.
SO PCT Int. Appl., 46 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C07C203-04
ICS C07D487-04; C07D209-28; A61K031-40; A61K031-405; A61K031-21
ICI C07D487-04, C07D209-00
CC 25-24 (Benzene, Its Derivatives, and Condensed Benzenoid Compounds)
Section cross-reference(s): 1, 23
FAN.CNT 2

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9509831	A1	19950413	WO 1994-EP3182	19940923
W: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, JP, KG, KP, KR, KZ, LK, LR, LT, LV, MD, MG, MN, NO, NZ, PL, RO, RU, SI, SK, TJ, TT, UA, US, UZ, VN				
RW: KE, MW, SD, SZ, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
GB 2283238	A1	19950503	GB 1993-20599	19931006
GB 2283238	B2	19971126		
CA 2173582	AA	19950413	CA 1994-2173582	19940923

	AU 9478092	A1	19950501	AU 1994-78092	19940923
	AU 678063	B2	19970515		
	EP 722434	A1	19960724	EP 1994-928801	19940923
	EP 722434	B1	19980729		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, NL, PT, SE				
	HU 74446	A2	19961230	HU 1996-874	19940923
	HU 218923	B	20001228		
	BR 9407749	A	19970212	BR 1994-7749	19940923
	JP 09503214	T2	19970331	JP 1994-510585	19940923
	AT 168986	E	19980815	AT 1994-928801	19940923
	ES 2120070	T3	19981016	ES 1994-928801	19940923
	RU 2136653	C1	19990910	RU 1996-108907	19940923
	US 5700947	A	19971223	US 1996-624508	19960405
	US 5780495	A	19980714	US 1997-902570	19970729
PRAI	GB 1993-20599	A	19931006		
	IT 1994-MI916	A	19940510		
	WO 1994-EP3182	W	19940923		
	US 1996-624508	A3	19960405		

OS CASREACT 123:82961; MARPAT 123:82961

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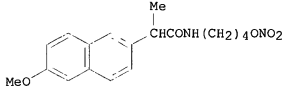

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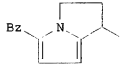

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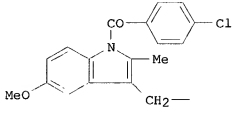

AB The title compds. MCOY[C(A)(B)]nONO2 [A, B = H, (un)branched alkyl; M = Q1, Q2, 2-(6-methoxy)naphthyl, etc.; n = 1-10], useful as analgesics, antiinflammatory agents, and blood platelet aggregation inhibitors, are prepd. Thus, 2-(6-methoxy-2-naphthyl)propionic acid was converted into its Na carboxylate salt with NaOEt, the salt condensed with 1-bromo-4-chlorobutane, and the 4-chlorobutyl 2-(6-methoxy-2-naphthyl)propionate intermediate nitrated by reaction with AgNO3, producing the 4-nitratobutyl ester, II.

ST nitratobutyl methoxynaphthylpropionate prepn analgesic; antiinflammatory prepn nitratobutyl methoxynaphthylpropionate

IT Analgesics
Blood platelet aggregation inhibitors
Inflammation inhibitors
(org. nitrate esters)

IT 164790-47-0P 164790-48-1P 164790-49-2P **170591-17-0P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **SPN (Synthetic preparation)**; THU (Therapeutic use); BIOL (Biological study); **PREP (Preparation)**; USES (Uses)

KATHLEEN FULLER EIC 1700/PARKER LAW 308-4290

(prepn. of org. nitrate esters having antiinflammatory and/or analgesic activity)

IT 110-52-1, 1,4-Dibromobutane 1074-82-4, Potassium phthalimide 6940-78-9, 1-Bromo-4-chlorobutane 7761-88-8, Silver nitrate, reactions 7789-60-8, Phosphorous tribromide 23981-80-8, 2-(6-Methoxy-2-naphthyl)propionic acid 74103-06-3, Ketorolac
RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn. of org. nitrate esters having antiinflammatory and/or analgesic activity from)

IT 5394-18-3P 38835-18-6P, 2-(6-Methoxy-2-naphthyl)propionyl chloride 55577-80-5P, Sodium 2-(6-methoxy-2-naphthyl)propionate 164790-50-5P 164790-51-6P 164790-52-7P 164790-53-8P 164790-54-9P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of org. nitrate esters having antiinflammatory and/or analgesic activity from)

IT **170591-17-0P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **SPN (Synthetic preparation)**; THU (Therapeutic use); BIOL (Biological study); **PREP (Preparation)**; USES (Uses)
(prepn. of org. nitrate esters having antiinflammatory and/or analgesic activity)

RN 170591-17-0 HCAPLUS

CN 2-Naphthaleneacetic acid, 6-methoxy-.alpha.-methyl-, 4-(nitrooxy)butyl ester (9CI) (CA INDEX NAME)